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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: COMPONENTS OF THE PRESENILIN-COMPLEX

(57) Abstract: The present invention is based on a novel direct interaction between a Presenilin and a novel protein identified herein and named Sambiasin-1, a homolog thereof named Sambiasin-2, as well as a protein complex further comprising a Nicastrin. Also comprised are uses of said components and complexes, as well as methods for use of the protein and the complex, inter alia, screening, diagnosis and therapy, as well as methods of preparing the complexes.

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07K14/47 G01N33/68 C07K19/00 A61K38/17

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07K G01N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

BIOSIS, EPO-Internal, EMBL, FSTA, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE EMBL 'Online! 23 May 2000 (2000-05-23) LIN W -C: "Homo sapiens CGI-78 protein mRNA, complete cds" retrieved from EMBL Database accession no. AF151835 XP002264708 the whole document -& LAI C -H ET AL: "Identification of Novel Human Genes Evolutionarily Conserved in Caenorhabditis elegans by Comparative Proteomics" GENOME RESEARCH, COLD SPRING HARBOUR LABORATORY PRESS, US, vol. 10, no. 5, 2000, pages 703-713, XP000929862 ISSN: 1088-9051 the whole document -& DATABASE SWISS-PROT 'Online! -/-</p>	9-13, 15, 17, 19, 21
T		

☒ Further documents are listed in the continuation of box C.☐ Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the International filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the International filing date but later than the priority date claimed

T later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	<p>15 September 2003 (2003-09-15) "Gamma-secretase subunit APH-1A (APH-1a) (Aph-1alpha) (Presenilin stabilization factor) (CGI-78)" retrieved from SWISS-PROT Database accession no. Q96BI3 XP002264709 the whole document</p>	
X	<p>KOPAN RAPHAEL ET AL: "Aph-2/nicastrin: An essential component of gamma-secretase and regulator of Notch signaling and presenilin localization" NEURON, vol. 33, no. 3, 31 January 2002 (2002-01-31), pages 321-324, XP002264651 ISSN: 0896-6273 the whole document</p>	<p>1-8,12, 13, 15-28, 30-37,41</p>
X	<p>YU G ET AL: "Nicastrin modulates presenilin-mediated notch/glp-1 signal transduction and beta-APP processing" NATURE, MACMILLAN JOURNALS LTD. LONDON, GB, vol. 407, 7 September 2000 (2000-09-07), pages 48-54, XP002173751 ISSN: 0028-0836 -& DATABASE GENE BANK 'Online! 8 September 2000 (2000-09-08) "Homo sapiens nicastrin mRNA, complete cds" retrieved from GENE BANK Database accession no. AF240468 XP002264715 the whole document</p>	<p>13</p>
P,X	<p>LEE SHEU-FEN ET AL: "Mammalian APH-1 interacts with presenilin and nicastrin and is required for intramembrane proteolysis of amyloid-beta precursor protein and Notch." JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 277, no. 47, 22 November 2002 (2002-11-22), pages 45013-45019, XP002264652 ISSN: 0021-9258 the whole document</p>	<p>1-8,12, 13, 15-28, 30-37,41</p>

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INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 03/06704

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	<p>GU YONGJUN ET AL: "APH-1 interacts with mature and immature forms of presenilins and nicastrin and may play a role in maturation of presenilin.nicastrin complexes." JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 278, no. 9, 28 February 2003 (2003-02-28), pages 7374-7380, XP002264653 ISSN: 0021-9258 the whole document</p> <p style="text-align: center;">---</p>	<p>1-8,12, 13, 15-28, 30-37,41</p>
P,X	<p>KIMBERLY W TAYLOR ET AL: "gamma-Secretase is a membrane protein complex comprised of presenilin, nicastrin, aph-1, and pen-2." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 100, no. 11, 27 May 2003 (2003-05-27), pages 6382-6387, XP002264654 May 27, 2003 ISSN: 0027-8424 (ISSN print) the whole document</p> <p style="text-align: center;">---</p>	<p>1-8,12, 13, 15-28, 30-37,41</p>
P,X	<p>FRANCIS ROSS ET AL: "aph-1 and pen-2 are required for Notch pathway signaling, gamma-secretase cleavage of betaAPP, and presenilin protein accumulation" DEVELOPMENTAL CELL, vol. 3, no. 1, July 2002 (2002-07), pages 85-97, XP009022872 ISSN: 1534-5807 the whole document</p> <p style="text-align: center;">---</p>	<p>1-8,12, 13, 15-28, 30-37,41</p>
P,X	<p>EDBAUER DIETER ET AL: "Reconstitution of gamma-secretase activity." NATURE CELL BIOLOGY, vol. 5, no. 5, May 2003 (2003-05), pages 486-488, XP001156572 ISSN: 1465-7392 (ISSN print) the whole document</p> <p style="text-align: center;">---</p>	<p>1-8,12, 13, 15-28, 30-37,41</p>
T	<p>LAVOIE MATTHEW J ET AL: "Assembly of the gamma-secretase complex involves early formation of an intermediate subcomplex of Aph-1 and nicastrin." JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 278, no. 39, 26 September 2003 (2003-09-26), pages 37213-37222, XP002264656 ISSN: 0021-9258</p> <p style="text-align: center;">---</p> <p style="text-align: center;">-/--</p>	

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 03/06704

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>GOUTTE CAROLINE ET AL: "APH-1 is a multipass membrane protein essential for the Notch signaling pathway in <i>Caenorhabditis elegans</i> embryos"</p> <p>PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 99, no. 2, 22 January 2002 (2002-01-22), pages 775-779, XP002264706</p> <p>January 22, 2002</p> <p>ISSN: 0027-8424</p> <p>-& DATABASE GENE BANK 'Online! 18 May 2000 (2000-05-18)</p> <p>LAI, C-H: "CGI-78 protein 'Homo sapiens!'" retrieved from GENE BANK</p> <p>Database accession no. ADD34072</p> <p>XP002264710</p> <p>the whole document</p>	
A	<p>LEVY-LAHAD E ET AL: "CANDIDATE GENE FOR THE CHROMOSOME 1 FAMILIAL ALZHEIMER'S DISEASE LOCUS"</p> <p>SCIENCE, AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE,, US, vol. 269, 18 August 1995 (1995-08-18), pages 973-977, XP000616667</p> <p>ISSN: 0036-8075</p> <p>-& DATABASE GENE BANK 'Online! 23 August 1995 (1995-08-23)</p> <p>LEVY-LAHAD E ET AL: "Homo sapiens (clone F-T03796) STM-2 mRNA, complete cds" retrieved from GENE BANK</p> <p>Database accession no. L43964</p> <p>XP002264716</p> <p>the whole document</p>	
A	<p>CRUTS M ET AL: "THE PRESENILIN GENES: A NEW GENE FAMILY INVOLVED IN ALZHEIMER DISEASE PATHOLOGY"</p> <p>HUMAN MOLECULAR GENETICS, OXFORD UNIVERSITY PRESS, SURREY, GB, vol. 5, 1996, pages 1449-1455, XP001094396</p> <p>ISSN: 0964-6906</p>	
A	<p>MUMM JEFFREY S ET AL: "Notch signaling: From the outside in"</p> <p>DEVELOPMENTAL BIOLOGY, vol. 228, no. 2, 15 December 2000 (2000-12-15), pages 151-165, XP002264707</p> <p>ISSN: 0012-1606</p>	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/06704

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 14 (partially), 29, 38-40
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 14 (partially), 29, 38-40

Present claim 14 relate to a compound defined by reference to a desirable characteristic or property, namely to an antibody which binds a protein complex comprising Sambiasin and Presenilin or Nicastrin, and which does not bind the first protein or the second protein when uncomplexed.

Present claims 29 and 38-40 relate to a compound defined by reference to a desirable characteristic or property, namely modulating the amount of, activity of, or the protein components of the protein complex.

The claims cover all compounds having this characteristic or property, whereas the application does not provide support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for any of them. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the claimed scope impossible.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.